

Running Head: HIGH FAT AND SUGAR DIET AND HIPPOCAMPAL INHIBITION

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A high-fat high-sugar diet predicts poorer hippocampal-related memory and a reduced ability to suppress wanting under satiety

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Abstract

Animal data indicate that greater intake of fats and sugars prevalent in a Western diet impairs hippocampal memory and tests of behavioral inhibition known to be related to hippocampal function (e.g., feature negative discrimination tasks). It has been argued that such high fat high sugar diets (HFS) impair the hippocampus, which then becomes less sensitive to modulation by physiological state. Thus retrieval of motivationally salient memories (e.g., when seeing or smelling food) occurs irrespective of state. Here we examine whether evidence of similar effects can be observed in humans using a correlational design. Healthy human participants ($N = 94$), who varied in their habitual consumption of a HFS diet, completed the verbal paired associate (VPA) test, a known hippocampal-dependent process, as well as liking and wanting ratings of palatable snack foods, assessed both hungry and sated. Greater intake of a HFS diet was significantly associated with a slower VPA learning rate, as predicted. Importantly, for those who regularly consumed a HFS diet, while reductions in liking and wanting occurred between hungry and sated states, the reduction in wanting was far smaller relative to liking. The latter effect was strongly related to VPA learning rate, suggestive of hippocampal mediation. In agreement with the animal literature, human subjects with a greater intake of a HFS diet show deficits in hippocampal-dependent learning and memory, and their desire to consume palatable food is less affected by physiological state – a process we suggest that is also hippocampal related.

Keywords: hippocampus, diet, wanting, Western diet, memory, liking, sugar, fat

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The rise in obesity in many countries has been linked to the increased consumption of a Western-style diet, one rich in saturated fats and refined sugars, and low in fiber, fruit and vegetables (Drewnowski, 2007). While this type of diet may contribute to weight gain via its palatability and energy density, it may have other effects as well. A recent animal-based model of obesity proposes that such a diet adversely impacts certain centrally controlled aspects of food intake regulation via memory and inhibition processes, which then directly contribute to weight gain (Davidson, Kanoski, Walls & Jarrard, 2005). Specifically, diets rich in saturated fat and refined sugar impair the ability of the hippocampus to appropriately inhibit food-related memories under a sated physiological state, which subsequently promotes energy regulation and thus obesity (Davidson et al., 2005). Animals consistently show robust impairments in hippocampal-related learning and memory following a shift from standard lab chow to a diet high in fat (e.g., Morrison et al. 2010; Greenwood & Winocur, 1996), sucrose (e.g., Jurdak & Kanarek, 2009; Kendig, Boakes, Rooney & Corbit, 2013), and both saturated fat and refined sugars (e.g., Beilharz, Maniam & Morris, 2013; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Tran & Westbrook, 2015). While the animal data are substantial, there has been relatively little translation into human research. So far, it has been established that greater consumption of a saturated fats and refined sugars – a HFS diet – is associated with poorer performance on hippocampal-related measures of learning and memory in children (Baym et al., 2014) and adults (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011) and with smaller hippocampal volume in the elderly (Jacka, Cherbuin, Anstey, Sachdev & Butterworth, 2015). These correlational findings suggest that as in animals, such a diet may impair hippocampal function across the lifespan.

The hippocampus may mediate several different regulatory functions in respect of food intake. These include: (1) explicit retrieval of what has been eaten to aid conscious

modulation of food intake (Higgs, 2002; Robinson et al., 2013); (2) integration of physiological signals of hunger, fullness and thirst, with memory for what has recently been eaten and drunk, to generate interoceptive states (Brannigan, Stevenson & Francis, 2015; Brunstrom et al., 2012); and (3) state-dependent retrieval and inhibition of pleasant food-related memories (Davidson et al., 2005; Davidson, Sample & Swithers, 2014). It is this last proposed mechanism that is of principal interest here, because of its apparent importance in modulating appetite according to hunger state.

It has been suggested, again on the basis of animal data, that upon encountering food cues when hungry, pleasant food-related memories associated with the cue are excited or retrieved, thereby motivating the animal to eat that food. However, when sated, such associations are inhibited, thus reducing the incentive to consume. The regulation of appetitive behaviour is therefore based on the ability of satiety cues to inhibit this association, and this ability depends on the functional integrity of the hippocampus (Davidson et al., 2005; Davidson, Sample & Swithers, 2014). It follows then that successful long-term energy regulation involves integrating physiological states (hunger/satiety) with these memory-driven motivational states, so as to facilitate or retard energy intake when encountering food cues in the environment. According to Davidson et al. (2005), diets high in fats and refined sugars disrupt this process by impairing hippocampal function. The latter would then impair the ability of satiety to inhibit pleasant food-related memories in the presence of palatable food cues, and hence the ability to modulate the incentive salience of food based upon physiological state. While animal data supports this type of model (e.g., Davidson et al., 2012; Murray et al., 2009), there is as yet no test of it in humans. The main focus of this current study is to provide such a test.

Liking a food when eating it (i.e., palatability) and wanting a food on seeing it (i.e., incentive salience) are key drivers of human eating behavior (Finlayson, King & Blundell, 2007). Wanting is hypothesized to be the consequence of an active process whereby internal

cues to bodily state and external cues to food are transformed into representations with an assigned motivational value (Berridge, 1996). Generating a ‘want’ is therefore highly dependent upon memory, with each food cue leading to the retrieval of its own particular sensory and hedonic attributes. While wanting may be heavily dependent upon memory, liking is likely to be far less dependent, because here *consumption* directly activates sensory-driven pleasure circuits (i.e., for sweetness, saltiness, fatty mouthfeel). Accordingly, wanting for a food should be strongly linked to hippocampal-related memory processes, while liking should not.

Another important consequence of this definition of wanting by Berridge (1996) is that the motivational value of a food should vary as a function of physiological state – a phenomenon termed ‘alliesthesia’ (Cabanac, 1971). While Cabanac (1971) defined this phenomenon using pleasantness (i.e., liking), others have since shown that changes in internal state induce greater decreases in wanting than liking when exposed to olfactory stimuli (Jiang et al., 2008) and visual stimuli (Finlayson, King & Blundell, 2007b). According to Davidson et al., (2005), the presence a food cue activates the stored representation of that food when hungry, but is inhibited when sated. Therefore, wanting should be more sensitive than liking to changes in physiological state, since wanting is driven by the integration of physiological state *and* by the activation of a food-related memory (Berridge, 1996), while liking involves only the former. To see then if wanting is less effectively modulated by state in habitual consumers of a HFS diet (and changes in liking are not), we asked participants to evaluate their desire to consume and their liking for palatable snack foods (Palatable food cue task) when hungry and later, after an experimental lunch, when sated. Our major prediction was that changes in wanting from a hungry to a sated state would be smaller in habitual consumers of a HFS diet than comparable changes in liking. In addition to ratings of liking and wanting, we also obtained salivary responses to these foods, which we expected to mirror changes in wanting.

To see if state-dependent effects on wanting and liking in the Palatable food cue task were associated with performance on a hippocampal-related task, participants were also given a second test. This involved learning pairs of words - verbal paired associates (VPA) – a task that is known to be dependent upon an intact hippocampus (Baxendale, 1995; Eichenbaum & Bunsey, 1995; Karantzoulis, Scorpio, Borod & Bender, 2012). Not only did we expect VPA performance to be poorer in frequent consumers of a HFS diet as predicted by our earlier work (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011), we also expected that VPA performance would correlate with size of the state-dependent change in wanting but not liking.

Following VPA training and testing, participants were asked to engage in a series of further learning trials which involved either explicit inhibition of some verbal paired associates and explicit rehearsal of others - the ‘Think/No think’ task. It has been claimed that performance on the ‘Think/No-Think’ task is also related to the hippocampus (Anderson & Green, 2001; Anderson et al., 2004). We thus predicted that performance on this task should also be poorer in frequent consumers of a HFS diet.

A further feature of this study was our attempt to recruit participants of normal BMI ($\leq 25\text{kg/m}^2$), as well as controlling for variation in BMI, since increased BMI may affect memory recall (De Wit et al., 2016). Several other factors can affect hippocampal function. These include age (e.g., Bouchard et al., 2008), gender (e.g., Cosgrove, Mazure, & Staley, 2007), physical activity (e.g., Erickson et al., 2011), sleep quality (e.g., Reimann et al., 2007), and depression and stress (e.g., Videbach & Ravnkilde, 2004). Furthermore, diet quality, food intake and attitudes to food and eating have been linked with gender (e.g., Northstone, 2012), sleep quality (e.g., Chaput, 2013), physical activity (e.g., Drewnowski & Evans, 2001), and depression and stress (e.g., Appelhans et al., 2012). These possibly confounding factors were also measured in this study.

Assessment of participants' diets used a validated food frequency questionnaire, designed to indicate differences in intake of saturated fat and refined sugar, the Dietary Fat and Sugar questionnaire (DFS: Francis & Stevenson, 2013). In addition, we also assessed skin carotenoid levels using a spectrophotometer to determine fruit and vegetable intake (Stephen, Coetzee & Perrett, 2011). This measure was expected to be negatively correlated with scores on the DFS. It also allowed us to test whether the *absence* of fruit and vegetables (rather than the *presence* of saturated fat and refined sugar) was associated with any hippocampal-related effects, on the grounds that a healthy diet may be protective.

In sum, the primary aims of the current study were to determine if more frequent consumption of a HFS diet impairs state-dependent changes in wanting but not liking, and to see if this effect is linked to hippocampal-related processes. Secondary aims were to determine whether a hippocampal-related measure of learning and memory (VPA) was acquired more slowly in frequent consumers of a HFS diet and whether this also extended to the Think/No-Think task.

Method

Participants

People differ in the degree to which they eat a HFS diet. As we wished to use a correlational approach in our analyses, we needed to ensure that we had sufficient numbers of people who rarely or frequently consumed a HFS diet. To this end we screened a large sample and recruited people only from the upper and lower quartiles of a measure designed to assess dietary intake of fats and refined sugars (more below). Having sampled in this way - and knowing that there would be some regression to the mean when peoples dietary habits were measured again during the study – we treated the dietary data as a continuous variable (i.e., a correlational approach) rather than grouping participants into 'highs' and 'lows'. This decision was made because the continuous approach under these circumstances is

considerably more powerful than the grouping approach (MacCallum et al., 2002; Preacher et al., 2005), as it uses all of the available information.

Participants were recruited via two routes. The first involved screening the participant pool maintained by the Department of Psychology at Macquarie University using the DFS, which is a 26-item food frequency questionnaire (score range from 26 to 130) designed to identify variability in intake of saturated fat and refined sugar. The DFS has good test-retest reliability ($r = .84$ over 22 weeks), and has been validated against a full-length food frequency questionnaire and a 4-day diet diary, for both saturated fat and refined sugar intake (Francis & Stevenson, 2013). Cut-offs for the DFS were similar to Francis and Stevenson (2011), with scores above 70 and below 55 being used to identify potential participants. A total of 651 undergraduates completed the DFS. Of these 267 remained as potentially eligible participants, since they met all of the following criteria: (a) fell above or below the cut-offs; (b) reported a BMI between 17 and 26 (broader than the conventional criteria because this was a self-estimate and as we included people of both Caucasian and Asian descent); (c) were aged between 17 and 35; and (d) consented to be approached.

The second recruitment route drew upon the broader university community. Two types of advertisement were routinely placed around campus, with one featuring fruits and vegetables and the other highly palatable snack foods. When a potential participant phoned to enquire about the advertisements, they were asked to report consumption frequencies for the seven items from the DFS that had the highest item-total correlations (Soft drinks; Cakes & Cookies; Pizza; Fried chicken, or chicken burgers; Doughnuts, pastries, croissants; Corn chips, potato chips, popcorn with butter; French fries, fried potatoes). Participants who met age and BMI criteria, and who scored below 16 or above 21 on this short-form DFS were potentially eligible to take part.

To determine whether a potentially eligible person was actually able to participate required a telephone-screening interview. This assessed any current health issues (physical or

mental illness; chronic conditions; recent hospitalizations; any history of eating disorders; any head injuries; food allergies), any past health issues, and spoken English ability (i.e., for participants recruited via adverts this included leaving a voicemail message and undertaking the screening interview). Participants who reported anything beyond minor health complaints (which included asthma) or who could not adequately comprehend the interview were excluded. Eligible participants were instructed to breakfast as normal, and then refrain from eating in the 3 h before testing so as to arrive hungry for lunch, with sessions being booked to start at either 1100 for a 1200 lunch or 1300 for a 1400 lunch. Participants were also told that they could drink water in this period but not caloric beverages and that they were not to exercise beyond their normal pattern.

In total 97 participants completed the study. Of these 56 were from the psychology subject pool and 41 from the broader community. Data from three participants were excluded. One male participant revealed that they were diabetic and epileptic on the health-screening questionnaire administered at the start of the study. Two female participants had BMI's < 17 - one of 16.2 and the other of 15.2. Although neither reported having an eating disorder during telephone screening (nor to having a BMI under 17) nor on the health screening questionnaire, we were concerned that this BMI might point to significant under-nutrition, with unpredictable impacts on food-related behavior. The same pattern of significant findings was obtained even when these three participants were included. Demographic and other information about the 94 participants whose data were included in the reported analyses are given in Table 1.

Materials

The experimental lunch served during the study was either 350g of Beef Lasagne (Woolworths select brand: total energy 1930KJ [5.5% protein, 5.5% fat, 15.0% carbohydrate, by weight]) or if they disliked lasagne (prior to consumption), 350g of Spinach and Ricotta Ravioli (Woolworths select brand; 1640KJ [4.6% protein, 3.7% fat, 14.9% carbohydrate, by

weight]). Alongside this hot meal, participants were also presented with a plate of cookies, consisting of four chocolate Tim Tam biscuits (total energy 1596KJ [4.6% protein, 26.9% fat, 63.9% carbohydrate, by weight]) and eight Woolworths chocolate chip cookies (total energy 1744KJ [5.0% protein, 22.7% fat, 66.7% carbohydrate, by weight]).

The Palatable Food Cue task used eight snack-food items, four savory and four sweet. These were: (1) a cheese and bacon ball (Fritolay); (2) a 0.5 cm³ piece of cheddar cheese (Mainland); (3) a BBQ Pringles chip; (4) a salt and vinegar Pringles chip; (5) a piece of Flake chocolate (Cadbury Flake bites); (6) a mini Tim-Tam chocolate biscuit (Arnotts); (7) a mini chocolate chip cookie (Arnotts); and (8) a Malteser (Mars).

The 52 words for the paired associate tasks were selected from the lists in Nørby et al., (2010). All of the selected words were nouns with between 5 and 9 letters, emotionally neutral and occurring in the medium to high frequency range of the Corpus of Contemporary American English. From these 52 words, 26 pairs were formed that were not obviously related, which was achieved by randomly generating word pairs and then having the experimenters check for relatedness (see Appendix 1 for selected word pairs).

Procedure

The study protocol was approved by the Macquarie University Human Research Ethics Committee and written consent was provided by each participant. The study started with the completion of: (1) a questionnaire to check adherence to the pre-experimental instructions; (2) a health questionnaire to confirm the screening interview and to check for any common chronic diseases, current health, and basic medical history; (3) a brief sleep scale (the Pittsburgh Insomnia Rating Scale 2; Moul et al., 2002); (4) a depression, anxiety and stress scale (DASS-21; Lovibond & Lovibond, 1995); and (5) a physical activity measure (IPAQ-SF; Papathanasiou et al., 2010). To assess skin yellowness and thus carotenoid levels, two readings from the palm of each hand were obtained with a CM-700D Konica-Minolta Spectrophotometer, using the *b** axis measure (Stephen, Coetzee & Perrett, 2011).

Participants were then given the major study tasks in the following sequence: (1) The Palatable Food Cue task while hungry; (2) Verbal Paired Associates training followed by the Think/No-Think task, and then lunch; and (3) the Palatable Food Cue task while sated. Each of these tasks, and the lunch meal, were accompanied by additional measures (detailed below), most notably ratings of how hungry, thirsty, full, happy, sad, relaxed and alert they were - in that order - on 120mm line rating scales (anchors Not at all and Very). These ratings were repeated at various intervals throughout the session and are referred to as the hunger/mood ratings set.

Palatable Food Cue task (hungry). After completing the hunger/mood rating set, participants were instructed to place two pieces of sterile dental wadding around their submaxillary and sublingual salivary ducts (under the tongue), as well as placing one piece around each parotid duct (one each side of the upper jaw). The time elapsed from when the final piece of wadding was inserted until the time the last piece was removed was recorded. With the dental wadding in place, participants were then asked to touch, sniff and lick (in that order) each of eight snack food items presented in randomized order. Once participants had completed their interaction with all items they removed the wadding from their mouth and placed it into a bag for weighing.

After participants had rinsed their mouth with water they were presented with a fresh set of the eight snack food items, again in randomized order. Starting with the first item, participants were asked to look at it and judge how much they wanted to eat it using a 120mm line rating scale (anchors Not at all and A lot). This formed our measure of food wanting based solely upon viewing the sample.

They were then asked to taste the sample after which they made two further ratings, both on 120mm line rating scales: (1) How much did you like this food? (anchors Not at all and A lot); and (2) How much more of this food would you like to eat now? (anchors None and A lot). The first of these two ratings formed our measure of liking. The second rating

assessed immediate desire for more based upon sensory experience (in contrast to the wanting measure obtained prior to sampling the food that must be based upon memory). Following a water rinse, participants then repeated this process for each of the remaining snack food items.

Verbal Paired Associates (VPA). Before participants started this phase they were asked to complete a second set of hunger/mood ratings. The VPA task started with an initial presentation block composed of 26 trials. In each trial a word pair was presented on the computer screen for 5 s (e.g., table legend). Participants were instructed to read each word pair out loud and try to learn it. In the subsequent four training blocks only the first word of each pair was presented for 5 s (e.g., table), and participants were instructed to say out loud the (not shown) associated word. If they failed to respond within 5 s or their response was incorrect, the correct associate was presented (i.e., legend) and participants were instructed to say the pair out loud. The number of errors was recorded for each training block. The presentation order of the 26 trials was randomized in the initial presentation block and in each of the training blocks.

Think/No-think task. Following completion of the VPA task, the Think/No-Think training started. The 26 pairs used in the VPA task were randomly allocated to four sets: 2 ‘Practice’ pairs, 8 ‘Baseline’ pairs, 8 ‘Think’ pairs, and 8 ‘No-Think’ pairs. The two practice pairs were used to familiarize participants with the procedure. Participants were instructed that when they saw an initial word in green, they were to think of its associated word and to say it out loud (Think word). However, if they saw an initial word in red, they were instructed to suppress thinking of the associated word and to remain silent (No-Think word). No feedback was provided. The 8 Think and 8 No-Think initial words were then presented 7 times each (i.e., 112 trials). These 112 trials was organized into 7 blocks each composed of 16 trials, with each block composed of the 8 Think and 8 No-Think initial words, presented in randomized order. On each trial the initial word was displayed for 5 s, with a 1-s inter-trial interval. Participants then immediately undertook the first think/no-think test phase. The first

word of each of the 26 pairs was presented for 5 s, all in standard black font. Participants were told to recall out loud its associated word (including the ‘No-Think’ words). Order of presentation was random and no feedback was given. A second test occurred at the end of the study, as described later.

Lunch. Participants started by completing the third hunger/mood ratings set. They were then instructed to eat as much of the presented food as they wished and to ask for more if they were still hungry. They were also told that all uneaten food would be thrown away. *Ad libitum* access to cold water was provided throughout lunch.

During the lunch period participants were told not to use electronic devices (all belongings etc., being left in the laboratory vestibule), but were allowed to read magazines provided in the test room while eating. The content of these magazines had been screened to avoid any eating-related or upsetting material. After giving participants their food, the experimenter left the test room, returning 10 min later to see if they would like any more food and to ask the participant to call out when they had finished or if they wanted more. Uneaten food was then removed for later weighing.

Palatable Food Cue task (sated). After completing the fourth hunger/mood ratings set, participants undertook the Palatable Food Cue task again. This was identical to the first test in all respects, with salivation to the 8 snack food items measured first, followed by evaluation (want on looking), consumption, and evaluation (like and want on tasting), of each of the 8 snack food items.

Final measures. Participants started by completing the fifth and final set of the hunger/mood ratings. They were then given a delayed test for the 26 pairs learned earlier in the experiment. The test format was identical to that described above, except that a different randomized presentation order was used.

Participants then completed two questionnaires. The first was the 26-item DFS (Francis & Stevenson, 2013), so that a current measure of dietary saturated fat and refined

sugar intake was available for the analysis. The second was the 51-item Three-factor Eating Questionnaire, which has established reliability and validity (Stunkard & Messick, 1985), and which was used to collect data on participants' eating-related behaviors and attitudes. Finally, participants' height and weight were measured to assess BMI.

Analysis

Four sets of variables required square-root transformations so as to enable parametric analysis – the DASS scores (and the total score), participant age, the energy intake measures (and total energy intake), and the activity measure from the IPAQ.

On the VPA task, each participant had a percent correct score for each block and a learning rate score, calculated as percent correct on Block 4 minus percent correct on Block 1 (VPA Learning rate).

On the Think/No-Think task scores were derived from the two test phases, the initial and the delayed test, which took place at the end of the study. On each test, three scores were computed by calculating the percent correct responses for the 8 Think items, the 8 No-Think items and the 8 Baseline items. A further score was also derived, reflecting the overall magnitude of Think/No-Think related inhibition (collapsing across both tests; $[(\text{Think} + \text{Baseline})/2] - \text{No-Think}$).

Two sets of scores were computed for the Palatable Food Cue task, one for when the test was completed hungry and one when it was completed sated. On both occasions four measures were derived: (1) mean wanting on looking; (2) mean food liking after tasting; (3) mean want more scores after tasting; and (4) salivation rate (in grams per sec). For the first three scores, these were all averaged across the 8 snack food items, and for the fourth, only an aggregate score for all items was available.

Three approaches were taken to analyze these data. The first involved descriptive statistics and zero order correlations between the diet-related variables (i.e., DFS score and the spectrophotometer measure) and the demographic, control, interoceptive and eating-

related measures. The second approach was to analyze VPA, Think/No-Think, and Palatable Food Cue task data, with repeated measures ANOVA, to test for changes over time in outcome measures (i.e., VPA learning, Think/No-Think related inhibition, change in wanting/liking ratings with state). The third approach was to examine sources of variability in the VPA, Think/No-Think, and the Palatable Food Cue Task using stepwise regression analyses. It is this third approach that directly addresses the primary and secondary aims identified in the Introduction.

The selection of predictor variables for each regression model was based upon the following criteria. First, all models contained the main predictor of interest, the DFS diet score, along with basic demographic and control variables. Thus all models started with the following predictors: [1] age; [2] gender; [3] DASS total score (as the three sub-components were highly correlated); [4] PIRS sleep score; [5] activity score from the IPAQ; [6] Restraint score from the TFEQ; [7] Hunger score from the TFEQ; [8] Disinhibition score from the TFEQ; [9] BMI; and [10] DFS (diet) score. Second, this initial set of predictors was then included in a further regression analysis alongside the spectrophotometer measure, to establish whether this displaced the DFS (diet) score, indicating whether it was the absence of fruit and vegetables in the diet, rather than the presence of saturated fat and refined sugar, that might be predictive of performance. Third, for the Palatable Food Cue task regressions, amount of lunch consumed (total in kJ) and the change in hunger across lunch were added into all models, as participants varied in how much they ate and in how much hunger ratings changed across the meal. Fourth, on the two regression analyses establishing links between performance on the Palatable Food Cue Task and measures of hippocampal-related learning and memory, we included both our primary measure of hippocampal-related functioning, VPA Learning rate, as well as a secondary measure, namely the Think/No-Think related inhibition score. Finally, we note that it is generally advisable in regression to have at least 5-

10 cases per predictor variable, and while all our models fell above the lower bound, a higher ratio would have been more desirable.

Results

Participant characteristics, lunch, interoceptive and mood measures

Participant characteristics are presented in Table 1. There was a significant association between the DFS dietary score and the spectrophotometry measure. Participants reporting diets richer in saturated fat and refined sugar tended to have less yellow skin (beta values), indicative of lower fruit and vegetable intakes. There were some significant associations between participant characteristics, and the diet and spectrophotometry measures. Female participants tended to have lower DFS scores than men, and greater dietary restraint, as measured by the TFEQ. For females the latter was associated with lower DFS score and yellower skin.

Hunger, fullness and the lunch-related measures are detailed in Table 2. Both hunger and fullness ratings significantly changed across Time, $F(4,372) = 239.40$, $MSE = 361.32$, $p < .001$, partial eta-squared = .72, and $F(4,372) = 276.52$, $MSE = 380.30$, $p < .001$, partial eta-squared = .75, respectively. In both cases, there were highly significant linear trends across Time for decreasing hunger, $p < .001$ and for increasing fullness, $p < .001$. There were a number of significant associations between hunger and DFS score, and one with fullness, but none involving the spectrophotometer measure. Hunger ratings tended to be higher and fullness ratings lower in participants reporting a higher DFS score (i.e., more refined sugar and saturated fat).

For energy consumed at lunch, both overall, and for each food-type, there was a tendency for this to be higher in participants reporting a higher DFS score (p 's from .061 for total energy intake, .078 for biscuits and .42 for lasagne/ravioli intake).

We also assessed changes in thirst and mood across the study. For thirst, ratings changed across the study, $F(4,372) = 61.36$, $MSE = 492.80$, $p < .001$, partial eta-squared

= .40, with progressively decreasing thirst (linear trend, $p < .001$). For mood ratings, happiness ratings significantly increased across the study (linear trend, $p < .001$), sadness ratings decreased (linear trend, $p < .001$), and participants also reported feeling more relaxed (linear trend, $p < .01$). There were no significant changes in alertness ratings.

Verbal Paired Associates (VPA)

A one-way repeated measures ANOVA, with Block (first, second, third and fourth training block), entered as the within factor, revealed a significant main effect of Block, $F(3,279) = 327.22$, $MSE = 6.07$, $p < .001$, partial eta-squared = .78, with mean percent correct score increasing linearly across blocks (significant linear trend, $p < .001$; also noting a small cubic component, $p < .01$) – see Figure 1.

To determine whether VPA learning rate (percent correct on Block 4 minus percent correct on Block 1) was related to diet, we conducted a stepwise regression analysis. The dependent variable VPA learning rate, with predictor variables, DFS (diet) score, BMI, age, gender, IPAQ total activity score, DASS total score, PIRS sleep score, and Restraint, Hunger and Disinhibition scores from the TFEQ. The final model was significant and is presented in Table 3, with DFS (diet) score, TFEQ Disinhibition score, and DASS total score, as predictors. We then repeated this model, but now adding in the spectrophotometer score as a further predictor, but the same regression model emerged again (i.e., the spectrophotometer score was not predictive). Overall, these findings suggest a slower VPA learning rate is associated with higher reported intake of saturated fat and refined sugar (see Figure 1).

Think/No-Think task

A repeated measures ANOVA was conducted with Measure (Baseline vs. Think vs. No-Think) and Time (Immediate test vs. Delayed test) as within factors. The analysis revealed two significant effects. First, Measure, $F(2,186) = 6.59$, $MSE = 0.25$, $p < .005$, partial eta-squared = .07, with poorest recall in the No-Think condition, relative to the equally trained Think condition, and to the Baseline condition – see Table 4. Simple contrasts

revealed that the No-Think condition had the poorest recall, relative to the other two conditions (p 's $< .002$), which did not differ. Second, Time, $F(1,90) = 9.22$, $MSE = 0.34$, $p < .005$, partial eta-squared = .09, with percent correct recall improving slightly from the initial to the delayed test (see Table 4).

We then tested whether performance on the Think/No-Think task (see Table 4 – but collapsing across the initial and delayed test), could be predicted by participants dietary self-reports and other variables, again using stepwise regression. The dependent variable was the memory inhibition score derived from the Think/No-Think task, with predictor variables as described above. The final model was significant with just one predictor remaining in the model, IPAQ total activity score – see Table 5. Repeating this model by adding in spectrophotometer scores did not change the outcome, which indicated that larger inhibition scores were observed in participants who reported greater levels of physical activity. Finally, we note that participants varied in how much they had learned the word pairs (on the VPA task) before starting the think/no-think task. However, we could find no evidence that this affected participants' memory inhibition effect.

Palatable Food Cue task

Self-report measures. Participant evaluations of the palatable foods were analyzed using a two-way repeated measures ANOVA, with State as one factor (Tested hungry vs. Tested sated) and Measure as the other (Want to eat [on looking] vs. Liking [after tasting] vs. Want more [after tasting]), with the data illustrated in Figure 2. The ANOVA revealed main effects of State, $F(1,93) = 175.96$, $MSE = 546.03$, $p < .001$, partial eta-squared = .65, and Measure, $F(2,186) = 143.65$, $MSE = 109.58$, $p < .001$, partial eta-squared = .61, which were qualified by an interaction between State and Measure, $F(2,186) = 54.08$, $MSE = 46.72$, $p < .001$, partial eta-squared = .37. To determine the source of the interaction effect, the three difference scores across State (Tested hungry minus Tested full) for each Measure (Want to eat [on looking] vs. Liking [after tasting] vs. Want more [after tasting]) were compared. As

suggested in the Introduction, want to eat scores on looking at the food fell significantly more with the change of State than liking scores, $p < .001$. Want more scores after tasting the snack also decreased more across State, than liking scores, $p < .001$. Finally, want more after tasting scores fell further across State than want to eat on looking scores, $p < .05$. So while all evaluations declined when tested sated, this decrease was greater for both wanting ratings than for the liking rating.

We then tested our primary aim, namely whether the state-dependent difference in wanting ratings made when *looking* at the food, relative to the liking rating made after tasting it, could be predicted by dietary variables. In addition to the predictor variables used before, two further predictors were now included: Change in hunger across lunch, and the amount of energy consumed at that meal. The final significant model, which included the DFS (diet) score, is presented in Table 6. Repeating this model by adding in spectrophotometer scores led to the same outcome, and this variable was not included in the final model. As illustrated in Figure 2, want to eat ratings - relative to liking ratings after tasting - were *less affected* by state in participants who consumed diets richer in saturated fat and refined sugar. To make this effect more vivid, in Figure 3 we present data (liking and wanting ratings made when hungry and replete) from just the dietary extremes of our sample – the top and bottom 20% on DFS (diet) score. As can be seen, want to eat on looking scores, relative to liking, change less across state in those who routinely eat the most saturated fat and added sugar. Thus state may be less able to moderate retrieval of pleasant food-related memories in participants who frequently consume diets rich in saturated fat and refined sugar.

Finally, we examined the sources of variability in the other major component of the Time by Measure interaction, namely the relatively larger decline in wanting more after tasting, relative to liking. The same stepwise regression approach was used with the same predictor variables. The final model was significant, $F(2,91) = 14.10$, $p < .001$, adjusted $R^2 = .22$, with two predictors remaining in the model. These were change in hunger, $Sr = .42$,

$Sr^2\% = 18.1\%$, $p < .001$ and sleep quality score, $Sr = .24$, $Sr^2\% = 5.5\%$, $p < .02$. Repeating this model by adding in spectrophotometer scores led to the same outcome, and this variable was not included in the final model.

Saliva measure. Salivation rate significantly increased between the hungry and sated tests from a $M = 0.038$ g/sec ($SD = 0.009$) to $M = 0.049$ g/sec ($SD = 0.011$), $t(93) = 12.21$, $p < .001$, $r^2 = .61$. We tested to see if change in salivation rate between the hungry and sated states could be explained by any of the predictor variables used in the preceding regression analyses, but there were no significant models.

We then checked to see if change in salivation rate across states was associated with the aggregate self-report measures (i.e., main effect of Time), after partialling out the amount of energy consumed at lunch and changes in hunger across the meal. Greater salivation in the sated state (relative to the hungry state) was associated with smaller reductions in liking and wanting (i.e., main effect of Time), $r_{12.34}(90) = -.22$, $p < .05$, providing some validation for the self-report ratings. The three parts of the interaction effect for the self-report data were not significantly associated with change in salivation rate between internal states (r 's $< .14$).

Relationship between VPA and Think/No-Think tasks and the Palatable Food Cue task

If hippocampal-related processes contribute to participants' desire to consume food via state-dependent inhibition of food-related memories, then performance measures from the VPA and Think/No-Think tasks should explain individual variability in changes in wanting and liking between the hungry and sated states. In addition, to the extent that such measures tap hippocampal process more directly than diet, they should displace diet-related predictors on the Palatable Food Cue task findings. To test this, we conducted two further regression analyses, examining each major component of the Time by Measure interaction from the Palatable Food Cue task. The primary hippocampal related predictor was VPA learning rate and the secondary predictor being Think/No-Think inhibition score, noting that these two variables did not significantly correlate, $r = -.05$.

The dependent variable for the first regression was the difference across states between the wanting rating made when looking at the food, relative to the liking rating made when eating it. As can be seen in Table 7, VPA learning rate during training was the best predictor, displacing DFS diet score from the model (contrast with Table 6). Repeating this model by adding in spectrophotometer scores led to the same outcome. Overall, this suggests that state-dependent changes in wanting scores when just *looking* at palatable food - relative to liking scores when that food is actually consumed – are strongly predicted by how quickly participants learned the verbal paired associates, which in turn was shown earlier to be associated with reported dietary intake of saturated fat and refined sugar.

Finally, we examined sources of variability in the other major component of the Time by Measure interaction, namely the relatively larger state-dependent decline in wanting more after tasting, relative to liking. This regression analysis produced the same outcome as the one described earlier (an identical model – predictors change in hunger and sleep quality), with no significant involvement of either hippocampal related performance measure.

Discussion

The primary question addressed by this study was whether state-dependent reductions in wanting for palatable snack foods (relative to state-dependent reductions in liking for palatable snack foods) were: (1) less affected in consumers of a HFS diet; and (2) mediated by hippocampal-related processes. Consistent with expectation, the difference between wanting and liking responses between the hungry and sated states was smaller for habitual consumers of a HFS diet. We also found, again as predicted, that these diet-related impairments in wanting according to state were significantly predicted by VPA learning rate but not by the memory inhibition score from the Think/No-Think task.

There were several important ancillary findings: (1) VPA learning rate was associated with greater consumption of a HFS diet, replicating previous findings of associations between tests sensitive to hippocampal-related function and diet in healthy young people (Brannigan,

Stevenson & Francis, 2015; Francis & Stevenson, 2011); (2) greater consumption of a HFS diet was associated with smaller changes in hunger and fullness, that is reduced interoceptive sensitivity also as observed before (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011); (3) greater energy intake on test lunch tended to be linked with greater HFS dietary intake (Francis & Stevenson, 2011); (4) reduced skin yellowness, indicating lower intake of fruits and vegetables, was associated with greater consumption of a HFS diet; and (5) skin yellowness was not a significant predictor of hippocampal-related processes, suggesting that the *absence* of fruits and vegetables was not a driving factor in diet-related cognitive performance. Finally, while we found that salivation rate was related to overall changes in wanting and liking between the hungry and sated state, it was not associated with diet or hippocampal-related processes.

While the present findings are consistent with evidence linking diet to hippocampal function in humans (e.g., Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011; Jacka et al. 2015), it is the links between diet, hippocampal memory performance and wanting that are of central importance. Specifically, those with a diet richer in saturated fats and refined sugars reported smaller changes in wanting scores across state *relative* to liking scores. Since wanting (i.e., incentive salience) has a memorial component and should vary as a function of physiological state, it is plausible that it is an impairment in this process, which is driving these smaller changes in wanting relative to liking across state in HFS diet consumers. We therefore suggest that, in line with the model proposed by Davidson et al. (2005), this finding reflects poorer inhibition of pleasant food-related memories when sated. We also predicted earlier that state-dependent changes in liking should be less affected by any adverse impacts to hippocampal-related learning and memory, as liking is driven more by the direct sensory experience of the food (Robinson & Berridge, 2000) rather than by any memories of it. Importantly, the change between states was significantly larger in wanting relative to liking, and this interaction was predicted by dietary intake of fats and sugars (see

Table 6) and performance on the VPA task (see Table 7) – suggesting hippocampal mediation.

One potential implication of the wanting and liking findings is that in habitual consumers of a HFS diet physiological state should have less regulatory importance, resulting in desire-driven eating whenever palatable food cues are encountered (e.g., Lowe & Butryn, 2007). Another potential implication of these findings relates to the ‘vicious-circle’ model of obesity (Davidson et al., 2005). Here, disruption of hippocampal inhibitory control over food-related behaviors can heighten the risk of further overconsumption of the same foods that initially contributed to hippocampal dysfunction, promoting weight gain. Findings from animals provide support for this model (Davidson et al., 2010; Kanoski, Meisel, Mullins & Davidson, 2007; Kanoski & Davidson, 2010). The present results are consistent with the vicious circle model of obesity and may aid understanding of appetite control and overconsumption. Nonetheless, while we argue here that a diet rich in saturated fat and added sugar impairs, via hippocampal processes, the ability to use satiety to inhibit pleasant food related memories, an alternative interpretation is also plausible. Individuals more prone to palatable food intake may be more likely to eat when sated and to choose high fat high sugar foods. While we suggest this latter possibility is plausible due to the correlational nature of our study, the former interpretation seems more likely given what is known from animal data.

An unexpected finding was that performance on the Think/No-Think task was unrelated to HFS diet intake and to VPA learning rate. Moreover, there was also no relationship between the changes in wanting/liking across state and memory inhibition score from the Think/No-Think test. If these processes are all mediated by the same brain area – and fMRI data suggests that memory inhibition on the Think/No-Think task *is* (Anderson et al., 2004) – we would expect performance on these measures to be related. Since such relationships were not observed, one possibility is that other neural processes may be important in the Think/No-Think task. There are two reasons for this assertion. First, while

state-dependent changes in wanting/liking do not require explicit instruction to occur, the Think/No-Think task involves explicit (i.e., strategic) direction to inhibit or rehearse stimuli. Second, the strategic nature of the Think/No-Think task has been illustrated experimentally, as substituting an associated word instead of suppressing it, leads to markedly different memory recall when tested later (Racsmay, Conway, Keresztes & Krajcsi, 2012; del Prete, Hanczakowski, Bajo & Mazzoni, 2015). Nonetheless, a further alternative explanation also needs to be considered in light of the fact that fMRI data indicates that performance on the Think/No-Think task is associated with hippocampal activation (Anderson et al., 2004). It is possible that the Think/No-think task may be insensitive to diet-induced affects relative to other hippocampal-related tasks (i.e., VPA). Indeed, this could be potentially important as it would imply that not all hippocampal-related measures are equally sensitive to diet-induced change.

The spectrophotometer findings suggest that the hippocampal-related memory performance is not linked to reduced intake of fruit and vegetables, but rather to greater consumption of a HFS diet. There are several implications from this finding. First, the inverse association between skin yellowness and scores on the DFS scale provide further external validity, as greater saturated fat and sugar intake is usually associated with reduced fruit and vegetable intake (Cordain et al., 2005; Kearney, 2010). While further research is required, this points to the potential utility of the spectrophotometer as a simple indirect measure of diet quality. Second, it suggests that it is the presence of saturated fat and added sugar – as in animals – that is problematic, rather than the absence of fruit and vegetables. This implies that a diet containing significant amounts of fruit and vegetables may not be protective against a diet that is also high in saturated fat and added sugar.

Several control variables emerged as significant predictors of either VPA learning rate, the Think/No-Think memory inhibition score or for the Food Memory Inhibition effect. While depression, stress, and anxiety have all been found before to be associated with

hippocampal volume and/or function (e.g., Videbach & Ravnkilde, 2004), four associations were more surprising. First, physical activity was associated with the Think/No-Think memory inhibition score. We included a measure of physical activity because this is known to increase hippocampal volume and function (Erickson et al., 2011; Pereira et al., 2007). This in turn would suggest that memory inhibition performance on the Think/No-Think task was in fact supported by the hippocampus, something we argued earlier was not in fact the case. However, physical activity is in fact associated with improvements across many cognitive domains and brain areas, and the largest effects (on meta-analysis) are seen for tasks that involve executive function (Hillman, Erickson & Kramer, 2008).

A second association was observed between TFEQ Disinhibition score and VPA learning rate. TFEQ Disinhibition was positively associated with BMI, TFEQ Restraint and TFEQ Hunger, all of which have been found before to relate to measures sensitive to hippocampal related measures of learning and memory (Brannigan, Stevenson & Francis, 2015; Francis & Stevenson, 2011). Third, we found that both increasing age and poorer sleep were associated with larger reductions in wanting (relative to liking) across state, effects that were unlikely to be related to hippocampal-related processes, since VPA learning rate was also included in this model. Thus older age and poorer sleep - in the context of a young and healthy sample - reflect some other as yet unknown factors associated with better food-related memory inhibition.

We have shown here that HFS dietary intake is not only associated with poorer hippocampal-related memory performance as indexed by VPA learning rate, but also with poorer inhibition of food-related wanting when sated. Our findings suggest that hippocampal related processes are involved in energy regulation apparently in much the same way as suggested by animal models (Davidson et al., 2005; Davidson et al., 2014), irrespective or not of whether habitual consumption of a HFS diet causes (or is a consequence of) poorer hippocampal function. While causality cannot be inferred here, the results from this study

provide the first piece of evidence in humans to parallel those from animals linking a HFS diet, impaired hippocampal function, less efficient state-dependent inhibition of food-seeking behaviors and hence enhanced susceptibility to excess energy intake.

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Table 1: Descriptive statistics and Pearson correlations between participant characteristics, DFS (diet) score and the spectrophotometer measure

Variable	Descriptive statistics	Variable's correlation with:	
		DFS (Diet)	Spectrophotometry
DFS (diet) score	M = 62.0, SD = 12.8, range 34-88		
Spectrophotometer	M = 15.8, SD = 1.8, range 11.3-20.2	-.21*	
Gender	40 men/54 women	.22*	-.17
Age	M = 20.3, SD = 3.6, range 17-34	-.19	.13
BMI	M = 22.3, SD = 2.6, range 17.2-27.9	-.15	-.02
DASS			
Depression	M = 3.5, SD = 3.6, range 0-18	-.14	.14
Anxiety	M = 2.9, SD = 2.6, range 0-10	-.01	.17
Stress	M = 4.8, SD = 3.6, range 0-16	-.02	.14
Total score	M = 11.2, SD = 8.1, range 0-35	-.05	.19
PIRS (Sleep quality)	M = 4.7, SD = 1.3, range 2-8	-.04	.13
Activity (Mins/day)	M = 79.1, SD = 87.5, range 0-573	.14	.04
TFEQ			
Restraint	M = 7.4, SD = 5.4, range 0-20	-.35*	.23*
Disinhibition	M = 6.5, SD = 3.0, range 1-14	-.06	.19
Hunger	M = 6.6, SD = 3.5, range 0-14	.16	.14

* $p < .05$

Table 2: Descriptive statistics for hunger and fullness ratings across the study and for eating-related variables from the study lunch

Time	Descriptive statistics	Variable's correlation with:	
Variable	Mean (SD)	DFS (Diet)	Spectrophotometry
Start of the study			
Hunger 1	68.1 (29.3)	.16	.14
Fullness 1	29.9 (25.5)	-.01	-.05
Prior to memory inhibition testing			
Hunger 2	64.2 (25.9)	.32*	-.07
Fullness 2	44.9 (24.9)	-.28*	.08
Prior to lunch			
Hunger 3	74.4 (26.4)	.31*	.00
Fullness 3	38.1 (22.8)	-.09	.11
Lunch consumption			
Lasagne/Ravioli kJ	1799.5 (506.5)	.09	.02
Biscuits kJ	772.3 (800.2)	.20*	-.06
Total kJ	2571.8 (974.0)	.21*	-.02
Post-lunch			
Change in hunger across meal (Hunger 3 – Hunger 4)			
	60.0 (30.9)	.19	.00
Hunger 4	14.4 (17.7)	.13	-.01
Fullness 4	95.7 (22.5)	-.13	.07
End of the study			
Hunger 5	13.5 (16.7)	.15	-.14
Fullness 5	100.0 (21.9)	-.15	.08

* $p < .05$

Table 3: Final stepwise regression model predicting Verbal Paired Associates learning rate
(final training Block [4] percent correct minus initial training Block [1] percent correct)

Model				
Predictor variables	$r =$	$Sr =$	$Sr^2\% =$	$p <$
1. (Spectrophotometer included) $F(3,90) = 7.89, p < .001$, adjusted $R^2 = .18$				
DFS (diet) score	-.29	-.28	8.1	.005
DASS total	-.21	-.28	7.8	.005
TFEQ Disinhibition score	.23	.28	7.6	.005

Table 4: Think/No-Think task testing scores

Measure	Initial test	Delayed test
	Mean % correct (SD)	Mean % correct (SD)
Think	65.0 (26.3)	66.3 (26.3)
No-think	58.8 (26.3)	61.3 (28.8)
Baseline	65.0 (27.5)	67.5 (27.5)
Inhibition effect*	6.2 (14.5)	5.6 (15.7)

* Calculated as $((\text{Think} + \text{Baseline})/2) - \text{No-Think}$

Table 5: Final stepwise regression model predicting the inhibition effect (collapsing across the initial and delayed tests) from the Think/No-Think task

Model				
Predictor variables	$r =$	$Sr =$	$Sr^2\% =$	$p <$
1. (Spectrophotometer included) $F(1,92) = 4.25, p < .05$, adjusted $R^2 = .03$				
Activity	.21	.21	4.4	.05

Table 6: Final stepwise regression model predicting the change in liking relative to the change in wanting to eat ratings across state (hungry minus full), on the Palatable Food Cue Task

Model				
Predictor variables	$r =$	$Sr =$	$Sr^2\% =$	$p <$
1. (Spectrophotometer included) $F(3,90) = 15.41, p < .001$, adjusted $R^2 = .32$				
Change in hunger	.38	.43	18.5	.001
PIRS (Sleep quality)	.35	.34	11.7	.001
DFS (diet) score	-.19	-.26	6.7	.005

Table 7: Final stepwise regression model predicting the change in liking relative to the change in wanting to eat ratings across state (hungry minus full), on the Palatable Food Cue Task, now including VPA learning rate and the inhibition score from the Think/No-Think task

Model				
Predictor variables	$r =$	$Sr =$	$Sr^2\% =$	$p <$
1. (Spectrophotometer included) $F(4,89) = 16.10, p < .001$, adjusted $R^2 = .39$				
VPA learning rate	.41	.36	13.0	.001
Change in hunger	.38	.36	13.0	.001
PIRS (Sleep quality)	.35	.35	12.0	.001
Age	.07	.17	2.9	.05

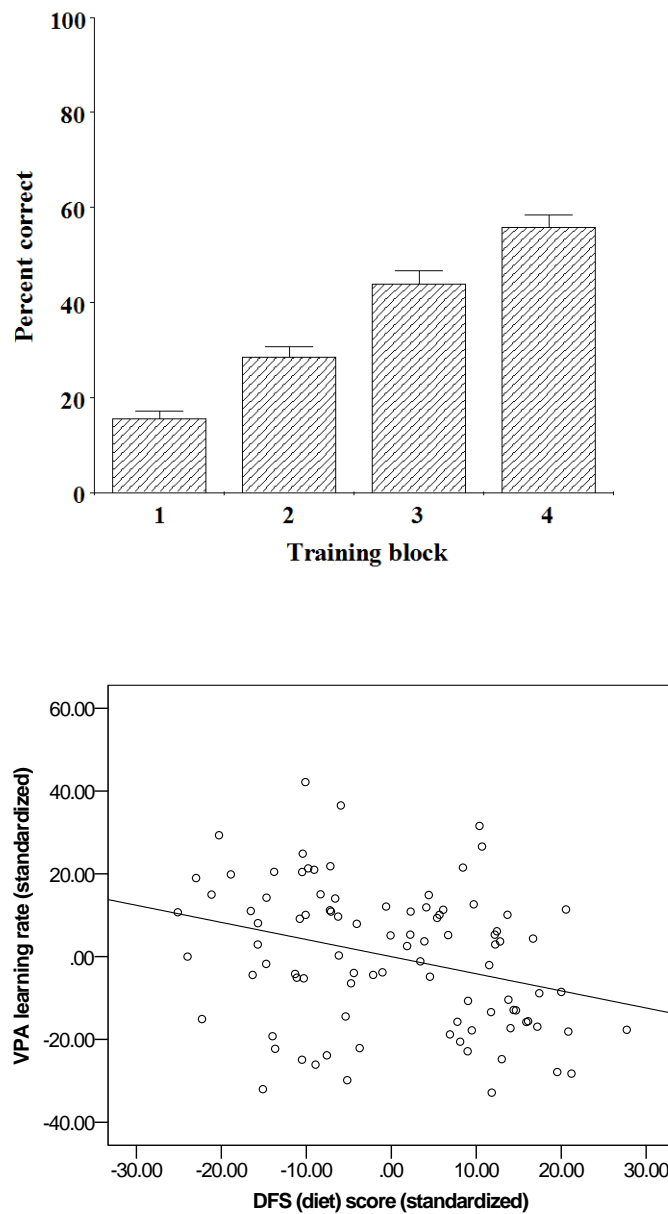


Figure 1: Top panel – Mean (and SE) learning rate on the VPA task for all participants (as percent correct) for each of the four training blocks; Bottom panel – Scatter plot of standardized DFS (diet) score and standardized VPA learning rate (Block 4 % correct minus Block 1 % correct) for all participants.

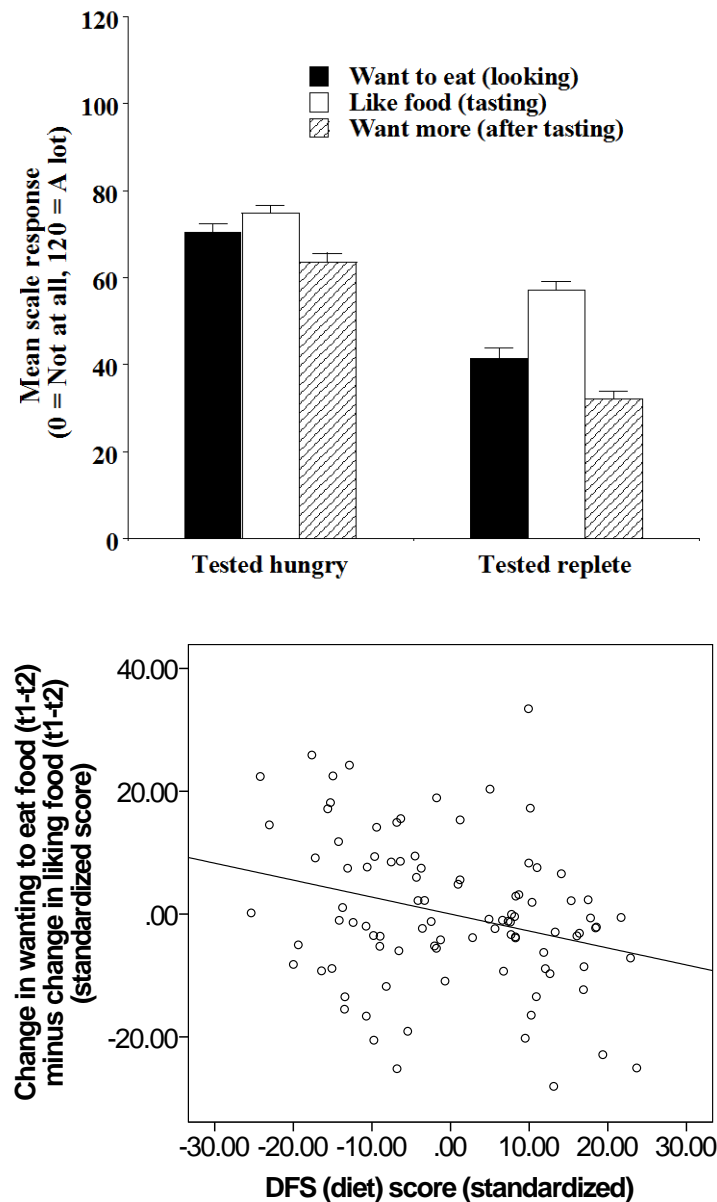


Figure 2: Top panel – Mean (and SE) wanting (on seeing), and liking and want more ratings (after tasting) in all participants obtained before and after lunch; Bottom panel – scatter plot of standardized DFS (diet) score and standardized change in wanting relative to liking across state (i.e., food memory inhibition effect) for all participants.

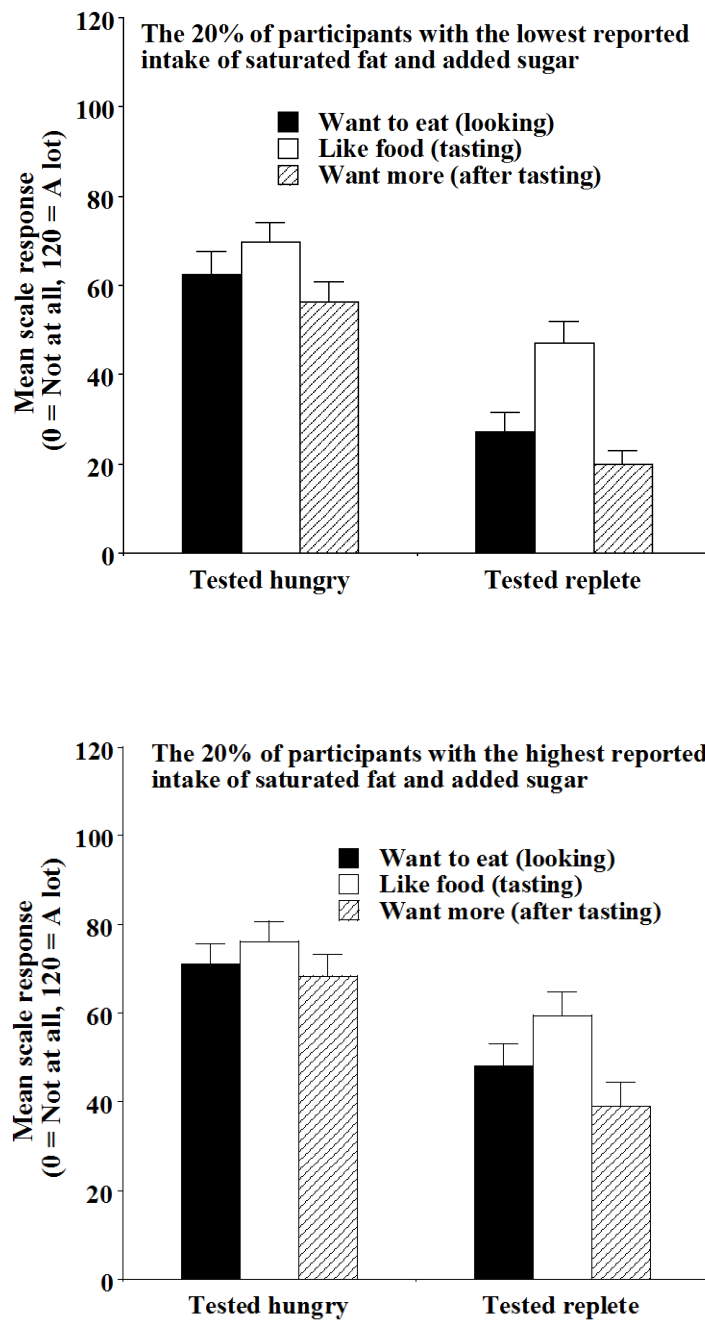


Figure 3: Top panel – Mean (and SE) wanting (on seeing), liking, and want more ratings (after tasting) in the 20% of participants with the *lowest* reported intake of saturated fat and sugar, obtained before and after lunch; Bottom panel – Mean (and SE) wanting (on seeing), liking, and want more ratings (after tasting) in the 20% of participants with the *highest* reported intake of saturated fat and sugar, obtained before and after lunch.

Appendix 1 – Word pairs used in the Memory Inhibition Task

1. Realism Entrance
2. Ruler Contrast
3. Juice Prelude
4. Curtain Subject
5. Precision Elephant
6. Leather Thicket
7. Handle Cabin
8. Summit Keyword
9. Bodywork Index
10. Business Piano
11. Fusion Storage
12. Trilogy Grant
13. Separate Penguin
14. Rider Capacity
15. Shower Patent
16. Prototype Freckle
17. Terrain Lecture
18. Counting Luggage
19. Table Legend
20. Briefcase Layout
21. Import Boarding
22. Compass Hearing
23. Habit Window
24. Stream Balcony
25. Bedding Elbow
26. Forecast Porridge